Research Article

LONG-TERM TOLERABILITY AND EFFECTIVENESS OF DULOXETINE IN THE TREATMENT OF MAJOR DEPRESSIVE DISORDER

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To examine the long-term safety, tolerability, and effectiveness of duloxetine in the treatment of major depressive disorder in a naturalistic study design meant to mimic clinical practice. Data were from the long-term, open-label, extension phase that followed a 12-week acute-treatment, multicenter study of adult outpatients with major depressive disorder. After the first week of the acute phase, all patients were treated with at least 60 mg daily duloxetine, which could be titrated to a maximum dose of 120 mg daily. Outcome measures were collected at monthly visits and included spontaneously reported adverse events, weight, vital signs, and the 17-item Hamilton Depression Rating scale. Seventy-two of the 177 (40.7%) patients who entered the extension phase of this study completed the study. The mean duration of participation in the extension was 305 days, with total exposure ranging from 68 to 707 days. Of the 177 patients who entered the extension, only 12 or 13 (7.0%) showed clinically significant worsening of depression that led to study discontinuation. The mean 17-item Hamilton Depression Rating scale score remained below 7 throughout the extension. A total of 21/177 patients (11.9%) discontinued due to adverse events during extension treatment. The adverse events causing discontinuation during the extension, with the exception of weight gain, were generally not unique to the extension phase, with 11/21 patients (52.0%) discontinuing due to adverse events that were first reported during acute treatment. Weight gain was reported as a reason for discontinuation during extension treatment in 4/177 (2.3%) patients. In this open-label study, efficacy was maintained for most patients. The adverse events causing discontinuation during the extension phase

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were generally not unique to the extension phase. Few patients experienced significant weight gain. Depression and Anxiety 25:E1–E8, 2008.

Key words: *safety; depression; long-term depression; antidepressive agents; antidepressive agents, second generation*

INTRODUCTION

The purpose of this paper is to examine the long-term safety, tolerability, and effectiveness of duloxetine. Duloxetine is a serotonin and norepinephrine reuptake inhibitor that is currently approved in the United States for treatment of major depressive disorder (MDD), diabetic peripheral neuropathic pain, and generalized anxiety disorder. It is also approved in several European countries for the treatment of stress-induced urinary incontinence.

This report presents data derived from the long-term extension phase that followed a 12-week acute-treatment study of MDD comparing the final stabilized dose of duloxetine within two treatment groups: (1) patients switched directly from their current antidepressant medication (citalopram, escitalopram, fluvoxamine, paroxetine, sertraline, or venlafaxine) to duloxetine 60 mg once daily; and (2) currently untreated patients who initiated duloxetine therapy at 30 or 60 mg once daily.

The results of the acute-treatment study showed that duloxetine improved depressive symptoms in both patient cohorts, and improvement did not differ significantly between groups [Wohlreich et al., 2005]. Acute-phase results from this study also showed that patients not taking an antidepressant before initiation of duloxetine tolerated duloxetine better if they started at a dose of 30 mg daily (for the first week) rather than starting at 60 mg daily (due to a lower rate of nausea), whereas patients switched directly from a selective serotonin reuptake inhibitor (SSRI) or venlafaxine to duloxetine could safely start at 60 mg once daily [Dunner et al., 2005]. No significant differences were found in the final stabilization doses across groups. After completion of the acute phase, 177 patients entered the open-label, long-term extension. The purpose of this report is to describe the outcome of these patients regarding maintenance of response and adverse events.

Effective treatment of MDD frequently requires long-term treatment. Continuation therapy of 16–20 weeks following remission is recommended for all depressed patients [APA, 2000], and maintenance therapy should be considered for many patients. Clinical trials in MDD treatment longer than 1 year are somewhat rare, and this study was instrumental in furthering our understanding of the safety and tolerability of long-term treatment with duloxetine.

MATERIALS AND METHODS

This study was an open-label, multicenter trial involving 29 sites in the United States. The study was designed to give the investigators a fair amount of flexibility with regard to dosing and timing of visits to best mimic clinical practice. All subjects participated with informed, voluntary consent, and the protocol was approved by the Institutional Review Board at each site. Patients were adult males and females, 18 years of age or older, who met DSM-IV criteria for MDD as their primary diagnosis. For study entry into the acute phase, patients were required to have a 17-item Hamilton Depression Rating scale [HAMD-17; Hamilton, 1960] total score of ≥ 15 and a Clinical Global Impressions-Severity of Illness (CGI-S) score of ≥ 4 (equating to a depressive episode of at least moderate severity) at visits 1 and 2.

Exclusion criteria for the acute-phase study included a diagnosis of bipolar disorder, schizophrenia, or other psychotic disorder; the presence of a primary Axis II Disorder; an unstable medical illness; serious suicide risk; treatment with fluoxetine within 30 days before beginning treatment; treatment with a monoamine oxidase inhibitor within 14 days before beginning treatment; lack of response in the current episode to two or more adequate trials of antidepressant therapy at an adequate dose for a minimum of 4 weeks, or meeting criteria for treatment-resistant depression; any anxiety disorder as a primary diagnosis within 6 months before the study entry; a history of substance abuse or substance dependence within 6 months before study entry; or a positive urine drug test at the screening visit.

Concomitant medications with primarily central nervous system activity were not allowed. Other medications, such as beta-blockers, diuretics, angiotensin converting enzyme inhibitors, antiarrhythmic, anticoagulants, and calcium channel blockers, were permitted under the condition that the patient had been on a stable dose for a minimum of 3 months.

The HAMD-17 was used to monitor MDD symptom severity throughout the study [Hamilton, 1960].

Safety measures included spontaneously reported adverse events, and changes in vital signs, weight, and laboratory tests. Elevated blood pressure was defined as supine systolic blood pressure ≥ 140 mmHg and at least 10 mmHg greater than baseline, or supine diastolic blood pressure ≥ 90 mmHg and at least 10 mmHg greater than baseline. Patients were

considered to have sustained hypertension if criteria for elevated systolic or diastolic blood pressure were met at three consecutive visits.

During the acute phase, 137 untreated patients were randomly assigned to receive 30 ($n = 67$) or 60 mg of duloxetine ($n = 70$), and 112 patients were entered into the acute phase of the study by means of switching from their antidepressant to 60 mg of duloxetine [Wohlreich et al., 2005]. After the first week, all patients were treated with at least 60 mg daily duloxetine, which could be titrated to a maximum dose of 120 mg daily. Patients who completed the 12-week study were offered entry into the extension phase, which is the focus of the present report. Dosages, as well as clinical and psychiatric measures of patients entering the extension phase, were examined by treatment group using a fixed-effect analysis of variance adjusting for investigative site. Summary statistics, unless otherwise indicated, are unadjusted and include all patients with non-missing values. In those cases where adjusted means are reported, they are derived from the mixed-model repeated measures model, which included the fixed effects of treatment group and investigative site and the random effect of linear and quadratic visit, the treatment group by linear visit and by quadratic visit. The number of days between visits among the patients becomes slightly more variable in extended longitudinal studies compared with short-term studies. It has been shown that if that variability is taken into account using mixed-model repeated measures model, more precise estimates of the mean can be calculated.

The extension phase continued until duloxetine was approved for MDD by the U.S. Food and Drug Administration and was commercially available, which occurred approximately 21 months after the earliest entry of patients into the extension phase. Data in the extension phase were collected at monthly visits. The last observation during the extension was used to determine response status.

RESULTS

One hundred seventy-seven subjects participated in the open-label extension phase. Of the patients who were not on antidepressant medication at the time they entered the acute phase, 48 were randomized to receive 60 mg of duloxetine daily and 46 were randomized to commence at 30 mg of duloxetine daily, increasing to 60 mg after 1 week; 83 patients were switched directly (without taper) from earlier SSRIs or venlafaxine to 60 mg of duloxetine daily.

Mean age (*SD*) was 43.7 (11.6) years. Most patients were female (71.2%) and most were Caucasian (87.6%). Patient groups were similar with four exceptions. There was a greater percentage of females in the switch group compared with the patients not receiving antidepressant treatment at baseline (30-mg treatment group) (67/83 [80.7%] versus 28/46 [60.9%]; $P = .021$). Extension patients not receiving antidepressant treatment at baseline (60-mg treatment group) were slightly younger on average than extension patients in the switch treatment group [41.7 (11.5) versus 45.2 (9.9) years, respectively; $P = .045$]. In addition, extension patients not receiving antidepressant treatment at baseline (60-mg treatment group) were slightly taller on average than extension patients in the switch treatment group [170.5 (8.8) versus 165.1 (10.7) cm; $P = .003$]. Finally, extension patients in the patients not receiving antidepressant treatment at baseline (60-mg treatment group) were slightly heavier on average than extension patients in the patients not receiving antidepressant treatment at baseline (30-mg treatment group) [85.5 (21.1) versus 77.0 (16.3) kg; $P = .013$].

Mean duloxetine dose at the beginning of the extension phase was 92.0 mg ($\pm$25.7). Two patients were at 30 mg (due to tapering before discontinuation), 53 at 60 mg, 53 at 90 mg, and 69 at 120 mg of duloxetine. The mean duration of participation in the extension was 305 days, and the range was 4–623 days. Because all extension patients also completed the 12-week acute phase, total exposure ranged from 68 to 707 days. Figure 1 shows the observed case analysis of the HAMD-17 scores at each visit up to 18 months (note that the sample size varies greatly from visit to visit and after, 18 months, significantly decreased due to study completion). The mean HAMD-17 score remained below 7 throughout the extension. Figure 2 shows the time course of continuation/dropout from the study. A total of 102 (57.6%) patients completed at least 1 year of treatment with duloxetine, and 58 (32.8%) patients completed 18 months of treatment with duloxetine. A total of 72 patients (40.7%) continued in the study for as long as the study allowed and completed participation in the study when duloxetine became commercially available.

Twelve-month completion of the extension phase was somewhat related to baseline treatment characteristics. Nineteen of the 46 untreated patients, who began at 30 mg of duloxetine, completed 12 months

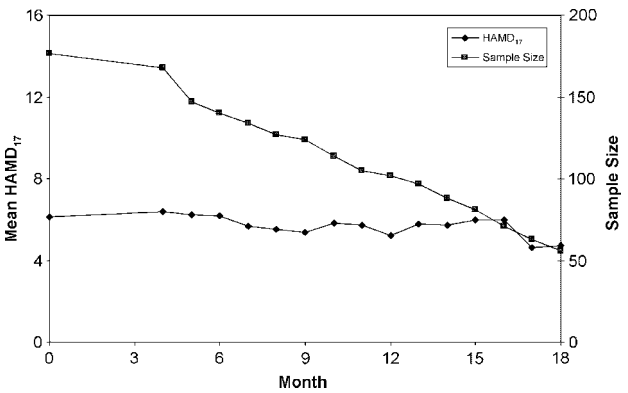

Figure 1. Observed case analysis of the HAMD-17 scores at each visit. HAMD-17, 17-item Hamilton Depression Rating scale.

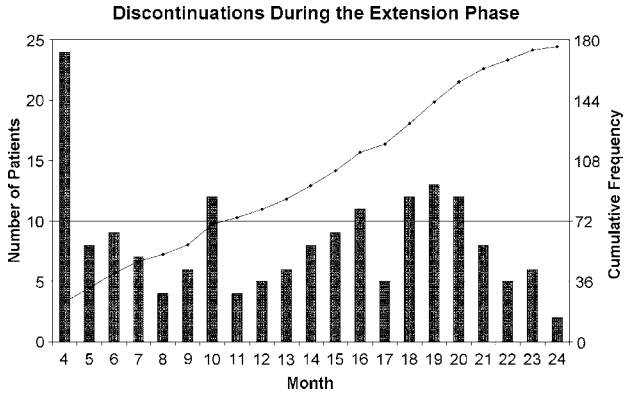

Figure 2. Time course of continuation/dropout.

(41.3%); 25 of 48 untreated patients, who began at 60 mg, completed 12 months (52.1%); 58 of the 83 switch patients completed 12 months (69.9%). Similar findings were noted only when women were considered: 13/28 30 mg—46.4%; 16/31 60 mg—51.6%; 47/67 switch—70.0%.

Of the 177 patients who participated in the extension phase, 119 began the extension in a remitted state; 27 began as responders; and 31 began as non-responders. Considering status at entry to the extension, patients tended to continue their entry clinical status or improve. Of the patients entering as non-responders, 13/31 (42%) remitted and 3/31 (10%) became responders during extension treatment. Of the patients entering as responders, 11/27 (41%) remitted and 9/27 (33%) became non-responders during extension treatment. Of the patients entering as remitters, 90/119 (76%) continued to be remitted; 13/119 (11%) became responders; and 16/119 (13%) became non-responders during extension treatment.

Six patients discontinued because of lack of efficacy (patient perception), and 12 patients discontinued because of lack of efficacy based on a decision made between the patient and the physician. Adverse events were associated with discontinuation in 21 patients; 36 patients discontinued because of "patient decision"; eight patients were discontinued due to protocol violations; 13 patients were lost to follow-up; six patients were discontinued because of "physician decision"; two patients were discontinued because of sponsor decision; and reason for discontinuation was not determined for one patient.

Of the 18 patients who discontinued due to lack of efficacy during the extension phase, five experienced essentially unchanged or improved HAMD-17 and Clinical Global Impressions-Severity of Illness values; one of whom had final HAMD-17 score of 8. A small increase in HAMD-17 score, 1–5 points, from the beginning to the end of the extension phase was seen in five patients, one of whom had a final HAMD-17 score of 6. Increases in the HAMD-17 score of over 5 points were noted in six patients. Data were not available for two patients. All but four of the discontinuations for "lack of efficacy" occurred within four visits of the start of the extension phase (by visit 13).

We evaluated discontinuation due to "patient decision" as to whether patients had actually worsened and possibly were discontinuing because of lack of efficacy. Of the 36 patients who discontinued because of "patient decision," 22 clinically improved from the beginning of the extension phase to the end of their participation, and 11 clinically worsened. Two patients remained the same (HAMD-17 of 0 for both patients). One patient had missing severity data. Of the patients who worsened, four had an HAMD-17 increase of 1 point (final scores of 6, 3, 3, and 3, respectively). One patient had a decrease of 10 points, and the remaining patients showed modest decreases from 2 to 9 points. Of the patients who discontinued because of "patient decision," four had final HAMD-17 scores of 10 points and 12 points, respectively. Only one patient had an HAMD-17 change of more than 10 points, with a final score of 19 points (this patient's decision to discontinue could have been related to a lack of efficacy).

Similarly, data from patients who discontinued due to "physician decision" were analyzed to see if this represented worsening of depression. Of the six patients, four showed worsening of their HAMD-17 scores. Two patients worsened by 17 and 13 points, respectively; one worsened by 8 points; and one patient worsened by 6 points. One patient improved, going from a HAMD-17 of 17 at the beginning of the extension phase to a score of 6 points at the end.

The adverse events causing discontinuation during the extension phase were generally not unique to the extension phase (Table 1). For the 21/177 (11.9%) patients who discontinued because of adverse events, nephrolithiasis, creatine phosphokinase increase, intentional self-injury, hypomania, rash, hypertension, suicidal ideation, and babesiosis were each reported by one patient in the extension but not during the acute phase. Weight increase was reported by two patients in the extension phase but not in the acute phase. In four patients, adverse events that were present in the acute phase continued and were reported as worsening, leading to discontinuation; these included fatigue, headache, night sweats, and decreased libido. Seven patients discontinued because of adverse events ongoing from the acute phase of treatment for which the severity of these adverse events in the extension phase was described as unchanged; these included dizziness in one patient and fatigue in one patient (both discontinued within a few weeks of beginning the extension phase); weight increase in two patients (which was stable during the extension phase); and diarrhea, anxiety, and fatigue in two patients.

We also assessed all the adverse events reported by patients during the extension phase to determine which were new to this phase and which were present from the acute phase and worsened, stayed the same, or improved. These data are present in Tables 2–4. In

TABLE 1. Relative severity of adverse events leading to discontinuation during the extension phase

Gender	Adverse event leading to discontinuation	First visit reported	Last visit reported	Severity compared with visit 9
Female	Anxiety	2	10	Same
Female	Babesiosis	28	28	New
Female	CPK increased	10	10	New
Female	Diarrhea	7	16	Same
Male	Dizziness	3	12	Same
Female	Fatigue	3	10	Same
Female	Fatigue	4	26	Worsened
Female	Fatigue	5	10	Same
Female	Headache	3	14	Worsened
Female	Hypertension	13	13	New
Male	Hypomania	10	10	New
Female	Intentional self-injury	9	10	New
Male	Libido decreased	4	16	Worsened
Female	Nephrolithiasis	15	15	New
Female	Night sweats	7	16	Worsened
Female	Rash	11	13	New
Male	Suicidal ideation	15	16	New
Female	Weight increased	2	20	Same
Female	Weight increased	9	22	Same
Male	Weight increased	14	19	New
Female	Weight increased	18	26	New

Note. Visits 1–9 were during the acute phase, and visit 10 and beyond were during the extension phase.
CPK, creatine phosphokinase.

TABLE 2. Clinically relevant adverse events reported as new or worsening in greater numbers than improved or remitted during the extension

Adverse event	Number of patients with new or worsening events	Number of patients with improved or remitted events
Aggression, irritability, anger, hostility	17	4
Dizziness	19	13
Abnormal dreams	10	0
Pain	8	5
Libido decrease	8	6
Weight increase	5	1
Suicidal ideation	5	3
Orgasm abnormal	4	2
Hypersomnia	4	1
Tremor	3	1
Night sweats	3	1
Balance disorder	3	1
Nightmares	3	2
Blood pressure increase	2	1
Weight decrease	2	0
Tachycardia	2	0
Hypomania	2	1
Early morning awakening	1	0

Note. 177 patients entered the extension.

TABLE 3. Clinically relevant adverse events reported as new or worsening versus improved or remitted occurring equally among patients during the extension

Adverse event	Number of patients with new or worsened events	Number of patients with remitted or improved events
Fatigue	16	16
Hyperhidrosis	8	8
Ejaculation delayed	1	1
Loss of libido	1	1
Urinary incontinence	1	1

Note. 177 patients entered the extension.

general, few patients reported new clinically relevant adverse events during the extension phase.

The adjusted mean increases from baseline in systolic blood pressure at 1.5 years were 1.26 and 2.24 mmHg for untreated at baseline and switch patients, respectively. The adjusted mean changes from baseline in diastolic blood pressure at 1.5 years were −0.13 and 0.49 mmHg for untreated at baseline and switch patients, respectively. Two patients met criteria for sustained hypertension. The adjusted mean increases from baseline in pulse at 1.5 years were 4.22 and 1.66 bpm for untreated at baseline and switch patients, respectively.

TABLE 4. Clinically relevant adverse events reported new or worsening less frequently than reported as improved or remitted during the extension

Adverse event	Number of patients with new or worsened events	Number of patients with improved or remitted events
Back pain	13	17
Vomiting	7	10
Anxiety	4	10
Middle of night insomnia	2	5
Asthenia	4	9
Depressed mood	4	6
Flatulence	2	7
Loose stools	2	5
Tinnitus	2	6
Palpitations	2	7
Nervousness	2	3
Panic attacks	1	2
Premenstrual syndrome	1	2
Hypercholesterolemia	2	4
Social phobia	0	2
Sexual dysfunction	0	2
Anorgasmia	1	3
Anorexia	2	6
Erectile dysfunction	1	4
Tension headache	2	7
Dysmenorrhea	1	9
Sedation	1	5

Note. 177 patients entered the extension.

The adjusted mean changes from baseline in weight at 1.5 years were 2.54 and 0.40 kg for untreated at baseline and switch patients, respectively (Fig. 3). To investigate whether these between-group differences in mean weight change were associated with differences in baseline clinical characteristics, body mass index at baseline was compared between groups. No statistically significant differences were observed between groups in body mass index at baseline. Three of the four patients who discontinued from the study due to weight gain were untreated at baseline. Of these three patients, two first reported weight gain during the extension phase, and one first reported weight gain at the last visit of the acute-treatment phase (after approximately 12 weeks of duloxetine treatment). One of the four patients who discontinued due to weight gain was switched to duloxetine after approximately 7 months of treatment with citalopram.

There was a significant difference between treatment groups in the overall distribution of patient-rated outcomes with respect to changes in sexual functioning during long-term treatment. Most SSRI switch subjects stayed the same or improved their sexual functioning during long-term treatment with duloxetine (approximately 70% stayed the same and 30% worsened), whereas 50% of currently untreated subjects at baseline

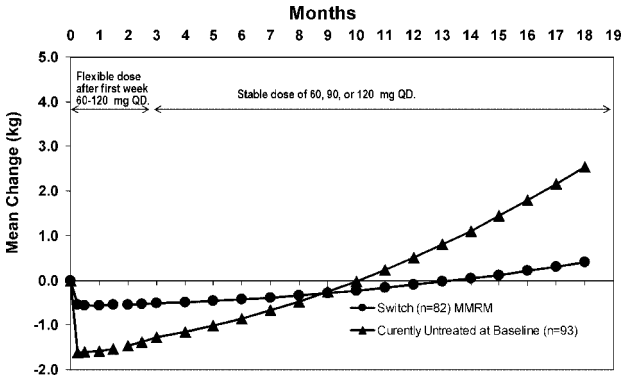

Figure 3. Time course of adjusted weight change in currently untreated patients at baseline and SSRI/venlafaxine switch patients. SSRI, selective serotonin reuptake inhibitor; QD, once daily; MMRM, mixed-effects model repeated measures.

improved and approximately 50% got worse during long-term treatment ($P = 0.17$ switch versus untreated). A separate paper focusing on the sexual functioning of these subjects is planned.

DISCUSSION

This study reports the results of long-term treatment with duloxetine in a large cohort of patients with MDD who completed an acute, 12-week treatment phase. To our knowledge, it is one of the longest treatment studies of depressive disorders reported, and therefore, comparative data are somewhat limited. Most extension studies, continuation or maintenance, are 1 year in duration. The maintenance study of imipramine versus psychotherapy by Kupfer et al. [1992] extended for 5 years. However, the number of patients who completed the study was small. Two studies of patients with chronic depression have been reported with continuation and extension phases of approximately 2 years. Gelenberg et al. [2003] reported results from a 52-week study of nefazodone versus placebo in the prevention of chronic depression. Keller et al. [1998] reported results from a 76-week maintenance-phase, efficacy study of sertraline versus placebo in chronic depression.

In this study, 72 of the 177 (40.7%) patients who entered the extension phase completed the study (ended participation when duloxetine became commercially available), with a total of 102 (57.6%) patients completing at least 1 year of treatment with duloxetine, and 58 (32.8%) patients completing up to 18 months of treatment with duloxetine. This is a relatively high percentage of patients given that the mean duration of antidepressant treatment in the United States is approximately 100 days. This figure has not changed appreciably over the past 10 years in spite of treatment guidelines that propose continuation-phase treatment for the first episode of depression, and maintenance treatment for patients with recurrent or chronic

depression [Depression Guideline Panel, 1993; NCQA, 2006; Simon et al., 1993]. In comparison, Keller et al. [1998] reported a 45% study completion rate for sertraline in a 76-week double-blind, placebo-controlled study, and Gelenberg et al. [2003] reported a 38% study completion rate for nefazodone in a 52-week double-blind, placebo-controlled study. Overall, effectiveness was maintained for most patients in our study. We found that some discontinuations, purported to be due to "lack of efficacy" may have been due to other reasons. Of the 18 (10.2%) patients who discontinued because of "lack of efficacy," four patients had no worsening in their clinical depression ratings, and five patients had only mild (1–5 increases on the HAMD-17) evidence of worsening depression. Eleven patients who dropped out because of "patient decision" clinically worsened; however, only one or two of these patients had clinically significant worsening on the HAMD-17. Of the patients who discontinued because of "physician decision," two showed significant clinical deterioration, and another worsened by 8 points. Thus, 12 or 13 (7%) patients out of the 177 patients who entered the extension showed clinically significant worsening of depression during the extension phase. These results are similar to results observed in a 52-week, open-label study of duloxetine at daily doses of 80 and 120 mg, which showed 5.9% discontinuation due to lack of efficacy [Raskin et al., 2003].

With regard to safety in the extension phase, no definitive pattern of adverse events emerged. The overall discontinuation rate due to adverse events was 11.9% in this study, which is comparable with 10.4% discontinuation due to adverse events reported in a sertraline study of similar length [Keller et al., 1998]. In this study, many events showed some overall improvement during the extension phase, including back pain, vomiting, and anxiety. The number of patients who showed new or worsening events in the form of aggression, irritability, or hostility was greater than the number who improved with these symptoms (22 versus four patients), but this reflects approximately 11% of patients. Furthermore, these events were not described as treatment-emergent mania. Dizziness was reported somewhat more frequently as worsening than improving; and abnormal dreams were rather unique as worsening versus improving in the extension phase. In contrast, events such as fatigue and hyperhidrosis were reported equally as new or worsening versus remitting or improved by patients. It should be noted that blood pressure changes and cardiovascular effects were not appreciably seen during the extension phase in contrast to the acute phase results. These results appear to be consistent with previous findings. Raskin et al. [2003] report that in a 52-week open-label study of duloxetine at daily doses of 80 and 120 mg, adverse events with an incidence of at least 5% after the initial 8 weeks of treatment were headache (10.0%), insomnia (7.3%), anxiety (7.3%), and dizziness (6.4%); and adverse events with an incidence of at least 2% after the initial 8 weeks of treatment were influenza and influenza-like illnesses, back pain, hypertension, increased weight, nasopharyngitis, and arthralgia.

As has been observed for other antidepressants, weight gain was observed for some patients in this study. Mean change from baseline for switch patients was minimal compared with the mean change for the untreated patients. The mean weight change at 18 months for switch patients showed an increase of 0.4 kg compared with 2.54 kg for untreated patients. The observed weight gain for untreated patients at 1.5 years in this study is similar to the increase of 2.1 kg observed in a 52-week open-label study of duloxetine at daily doses of 80 mg or 120 mg [Raskin et al., 2003]. In comparison, weight gain of 3.0–3.2 kg has been reported among depressed patients receiving either fluoxetine or placebo for a period of 50 weeks [Michelson et al., 1999]. Of the 21 patients who discontinued from the extension phase of this study due to adverse events, four patients discontinued due to weight gain, three due to fatigue, and no other adverse event was reported as a reason for discontinuation in more than one patient. Three of the four patients who discontinued from the study due to weight gain were untreated at baseline, whereas only one of the four patients who discontinued due to weight gain was switched to duloxetine after approximately 7 months of treatment with citalopram. For this patient, weight gain was reported at baseline and continued throughout treatment leading to eventual discontinuation. These results in conjunction with mean weight change results suggest that significant weight gain may be observed for some patients during long-term treatment with duloxetine, and patients without a recent history of SSRI use before treatment with duloxetine may be more susceptible to weight gain during long-term treatment.

Sexual functioning during the extension phase will be discussed in detail in a separate publication. However, our data did not reveal any meaningful worsening in sexual functioning during the extension phase.

Limitations of the study include its open-label nature, making the ability to assess causality of the changes in outcome measures limited. It is clear that the cited reason for discontinuation may not have been entirely accurate in some patients. In this study, only the primary reason for discontinuation was reported, and in patients where multiple secondary factors may have contributed to discontinuation, the relative influence of each of these factors is unclear. In addition, when considering differential adverse event frequency of occurrence during acute or long-term treatment, it should be noted that some adverse events, such as dizziness, aggression, irritability, and hostility, could be associated with tapering and discontinuation of therapy. Discontinuation-emergent adverse events may confound the data for long-term treatment-emergent adverse events.

The uniqueness of the data is the unusually long duration of the study with ongoing measures of safety and efficacy in a cohort of patients with MDD.

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